

## Tacrine (tetrahydroaminoacridine; THA) and lecithin in senile dementia of the Alzheimer type: a multicentre trial

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### Abstract

**Objective**—To see whether combined treatment with oral tacrine (tetrahydroaminoacridine; THA) and lecithin improves the symptoms of patients with Alzheimer's disease.

**Design**—Multicentre double blind, placebo controlled, random order crossover trial with individual determination of maximum tolerated dosage and four month follow up.

**Setting**—Outpatient departments at six university neurological centres.

**Patients**—67 Outpatients (24 men, 43 women) aged 53-81 (mean 66 (SD 7.3)) selected according to the following criteria: probable Alzheimer's disease as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; absence of mood disorder; mini mental state score lower than 26; availability of a close relative able to complete questionnaires; and informed consent of the patient or his or her closest relative, or both.

**Interventions**—Mean of 114 mg tacrine or placebo daily plus 1200 mg lecithin daily given in three divided doses for one four week active treatment period and one four week control period without washout at crossover.

**Main outcome measures**—Cognitive state as assessed by Folstein's mini mental state rating scale, behavioural state as assessed by the Stockton geriatric rating scale, and overall state as assessed with a visual analogue scale rated by both the relative and the physician.

**Results**—Compared with placebo tacrine did not improve either the mini mental state score (mean 14.9 (SD 7.3) *v* 14.8 (7.3)) or the Stockton geriatric score (28.2 (15.7) *v* 28.7 (17.8)), but a slight and statistically significant improvement occurred in the physician's score on the visual analogue scale (6.3 (10.2) *v* 11.6 (17.9)). Seven patients dropped out. Six patients were excluded because of acute hepatitis and one withdrew for personal reasons not related to treatment. Two other patients developed acute hepatitis at the end of the eight week crossover trial and another during the follow up study. Twenty patients complained of gastrointestinal side effects.

**Conclusions**—Neither short term nor long term treatment with oral tacrine at dosages lower than 125 mg/day improves the symptoms of Alzheimer's disease. Moreover, these dosages may induce hepatitis (nine of 67 patients in this series).

### Introduction

The report by Summers *et al* that combined oral treatment with the cholinesterase inhibitor tacrine (tetrahydroaminoacridine; THA) and lecithin improves the condition of patients with Alzheimer's

disease<sup>1</sup> has attracted considerable interest. Some aspects of their study were criticised, however,<sup>2,3</sup> and we therefore undertook a pilot study with a comparable design in an attempt to reproduce their results.<sup>4</sup> It was a feasibility study of six patients, and we found a small improvement in mini mental state score and no hepatic side effects. These findings encouraged us to perform a multicentre study with a larger number of patients in order to assess the cognitive effects of tacrine as well as its side effects. This paper reports the results.

### Patients and methods

Outpatients who had never been admitted to an institution and whose mother tongue was French were selected according to the following criteria: probable Alzheimer's disease as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association<sup>5</sup>; Hachinski score below 4<sup>6</sup>; absence of mood disorder and depression as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R) and the Montgomery and Åsberg depression rating scale<sup>8</sup>; absence of reversible causes of dementia as judged by standard diagnostic procedures (computed tomography and blood screen)<sup>9</sup>; mini mental state score 25 or less<sup>9</sup>; absence of liver abnormality; and availability of a close relative able to complete questionnaires. Informed consent was obtained from the patient and his or her closest relative. The study was approved by the Pitié-Salpêtrière Hospital ethics committee.

Based on the inclusion criteria 67 outpatients (24 men, 43 women) with a mean age of 66 (SD 7.3) years (range 53-81) were admitted to the trial at six university neurological centres. Table I lists the characteristics of the participating patients in each centre and those of the entire study population.

**Protocol**—The study was a randomised double blind, placebo controlled crossover trial conducted simultaneously at the six centres. Subjects were selected according to the seven inclusion criteria and submitted to a two week washout period during which any drugs not allowed during the study were stopped. During the first week of each double blind period the maximum dose of tacrine or placebo tolerated was determined in each patient, and this was given for the three subsequent weeks. Subjects were randomly assigned to receive placebo or tacrine as the first treatment by means of permuted blocks of four units. No appreciable differences emerged between the two groups before treatment as regards age, sex, duration of dementia, or its evaluation (table II). With 60 patients and a two sided alpha risk of 5%, and assuming the absence of a correlation between the response to tacrine and the response to placebo, the study had a 75% chance of detecting a three point change in the mini mental state score.

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TABLE I—General characteristics of 67 patients with Alzheimer's disease from six French neurological centres. Except where stated otherwise values are means (SD in parentheses)

	Centre A (n=13)	Centre B (n=12)	Centre C (n=12)	Centre D (n=15)	Centre E (n=11)	Centre F (n=4)	Total (n=67)
Age (years)	67.2 (8.4)	70.2 (7.7)	66.5 (7.9)	64.9 (5.8)	61.7 (6.2)	63.3 (3.5)	66.0 (7.3)
No of women/No of men	9/4	9/3	9/3	8/7	6/5	2/2	43/24
Characteristics of dementia:							
No with familial history of dementia	9/12	5/8	3/11	3/13	1/11	—	21/55
Duration (years)	4.2 (2.3)	4.4 (1.2)	3.8 (2.1)	3.8 (2.2)	6.0 (4.2)	—	4.4 (2.6)
No with presenile dementia (dementia before age 65)	8/13	4/10	8/12	9/13	10/11	1/1	40/60
Severity according to DSM-III-R:							
No with mild disease	7	3	2	4	3	2	21
No with moderate disease	4	5	5	8	4	1	27
No with severe disease	2	4	5	3	4	1	19
Mini mental state score	16.3 (5.9)	13.6 (6.9)	9.8 (6.0)	15.5 (7.5)	11.0 (5.5)	9.0 (9.1)	13.2 (6.9)
Montgomery and Åsberg depression score	5.4 (4.1)	19.4 (3.5)	10.3 (5.7)	8.6 (4.7)	14.9 (5.2)	7.3 (1.9)	11.2 (6.7)
Serum creatinine (μmol/l)	79.9 (16.5)	89.4 (12.0)	86.9 (19.0)	88.7 (13.9)	91.6 (14.7)	88.0 (15.3)	87.2 (15.3)
Serum aspartate aminotransferase (IU/l)	18.2 (9.1)	15.4 (6.0)	14.2 (7.7)	18.1 (8.2)	18.0 (7.8)	7.3 (3.3)	16.3 (7.9)
Serum alanine aminotransferase (IU/l)	14.7 (7.6)	12.7 (4.8)	13.6 (6.7)	17.3 (8.6)	17.5 (7.6)	15.0 (10.2)	15.2 (7.4)

TABLE II—Comparability at baseline of study groups of patients with Alzheimer's disease given tacrine in first period and placebo in second (group 1) and placebo in first period and tacrine in second (group 2). Except where stated otherwise values are means (SD)

Baseline characteristics	Group 1 (n=34)	Group 2 (n=33)
Age (years)	65.8 (8.0)	66.2 (6.8)
No (%) of men	14 (41.2)	10 (30.3)
Duration of dementia (years)	4.1 (2.0)	4.8 (3.1)
Mini mental state score	13.2 (6.6)	13.6 (6.5)
Mattis dementia score	84.5 (32.3)	77.6 (36.4)
Stockton geriatric score	29.1 (17.6)	30.6 (18.0)
Cognitive difficulties score	87.5 (21.5)	86.1 (20.9)

**Trial drugs**—Oral tacrine (Synthèse et Recherche, Antony, France) was given three times a day at dosages ranging from 50 to 125 mg per day. Nine patients were given 75 mg a day or less, eight were given 100 mg, and 43 patients 125 mg. The mean dose of tacrine was 1.92 mg/kg (range 0.73–2.78 mg/kg). Throughout the study patients were also given three daily doses of 400 mg egg lecithin containing 95% phosphatidylcholine.

**Other treatments**—Ten patients were given benzodiazepine drugs as hypnotics, and this treatment remained unchanged throughout. Four patients were given antihypertensive drugs, two cholesterol lowering drugs, and one an oral hypoglycaemic. During the tacrine treatment period one patient was given haloperidol for psychotic symptoms, and three patients were given this drug during the placebo period. Eleven patients were given 10 mg domperidone per day for nausea or vomiting during the tacrine treatment period and three patients were given this agent during the placebo period.

**Evaluation**—For cognitive evaluation we used the Folstein mini mental state rating scale,<sup>9</sup> the Mattis dementia scale,<sup>10</sup> and a letter cancellation task. Patients were also evaluated with a 10 word recognition task and associated memory tests. For these last two tests alternative forms were used at each visit. In all the tests listed above high scores reflected less severe impairment. Changes in behaviour were assessed by the patient's close relative using the Stockton geriatric rating scale<sup>11</sup> and the cognitive difficulties scale.<sup>12</sup> In both cases a high score reflected more severe impair-

ment. Tolerance of tacrine was evaluated by direct questioning of the patient or his or her relative, or both, and by clinical examination on days zero, 28, and 56 of the trial. As hepatic and haematological toxicity has been reported with tacrine,<sup>13</sup> blood samples were taken for liver enzyme measurements and cell counts on days zero, 14, 28, 42, and 56. If moderate increases in liver enzyme activities occurred or clinical signs worsened the physician was free to make more frequent blood tests. Patients were excluded from the study when their liver enzyme activities reached three times the normal for the laboratory concerned. At the end of each double blind treatment period the physician and patient's relative each subjectively scored improvement and drug tolerance on separate 10 cm visual analogue scales graded zero to 100. The battery of neuropsychological tests took between 30 and 45 minutes. Clinical evaluations were performed at baseline and at the end of each treatment period. Before the study the main evaluation criteria chosen were the mini mental state score and the Stockton geriatric score.

**Biological tests**—For technical reasons tacrine was assayed only in the 22 patients living in Paris or its suburbs. On the day of the laboratory tests blood samples were taken before the morning dose of tacrine or placebo and the plasma frozen until assay. For the 22 subjects concerned plasma tacrine concentrations were assayed blind at the same time by high performance liquid chromatography with ultraviolet detection at 235 nm (unpublished). The level of sensitivity of the method was 25.2 mmol/l. The coefficients of repeatability were 10% and 9% at 1260 and 2520 mmol/l respectively.

**Statistics**—Results are expressed as means and standard deviation (SD). Percentages were compared by the Pearson  $\chi^2$  test. Two means were compared by the paired or unpaired Student's *t* test, as appropriate. The results of the crossover study were tested by analysis of variance.<sup>14</sup> All calculations were done with the statistical analysis system package.<sup>15</sup>

## Results

Seven patients dropped out of the trial (see below), and statistical analyses were therefore performed on the remaining 60. As all the patients who dropped out were in the group given tacrine first, we checked that this and the group given placebo first remained comparable as regards age, sex ratio, and initial scores in cognitive and behavioural tests. No appreciable changes were observed during the study in the groups given tacrine or placebo first as regards the scores in the cognitive and behavioural tests (table III). As analysis of variance showed no interaction in either group between the effect and period of treatment, the results for the two groups were pooled. The mean rise in the mini mental state score was 0.017 (95% confidence

TABLE III—Results of main cognitive and behavioural evaluations during crossover study of tacrine and placebo in 60 patients with Alzheimer's disease (group 1 given tacrine in first period (days 1–28) and placebo in second period (days 29–56); group 2 given placebo in first period and tacrine in second). Values are means (SD)

	Group 1 (n=27)			Group 2 (n=33)		
	Baseline	Day 28	Day 56	Baseline	Day 28	Day 56
Mini mental state score	13.9 (6.1)	15.6 (6.7)	15.8 (6.7)	13.6 (6.5)	14.1 (7.8)	14.3 (7.9)
Stockton geriatric score	28.9 (17.3)	28.1 (14.5)	27.0 (13.1)	30.6 (18.0)	29.9 (17.9)	29.0 (20.2)
Cognitive difficulties score	86.6 (22.6)	85.2 (19.1)	84.7 (21.0)	86.1 (20.9)	87.9 (19.0)	83.4 (24.4)
Mattis dementia score	90.1 (29.9)	95.0 (27.7)	92.6 (32.5)	77.6 (36.4)	81.4 (37.9)	82.2 (40.6)

TABLE IV—Main characteristics of patients with Alzheimer's disease and acute hepatitis

Sex and age (years)	Group*	Dosage		Day of treatment	Maximum serum aspartate/ serum alanine aminotransferase activities (IU/l)	Symptoms
		mg	mg/kg			
F 59	1	125	2.36	14	248/596	None
M 64	1	100	1.27	28	384/960	None
M 62	1	125	1.60	43†	135/133	None
M 68	1	75	0.99	34†	35/85	Acute confusion
F 61	1	50	0.77	26	161/259	None
F 76	1	75	1.39	20	1845/2115	Fever, jaundice
F 58	2	75	1.47	56	115/242	None
F 74	2	125	2.55	56	100/136	None
F 61	Follow up study	125	1.81	4 Months	42/208	None

\* Group 1 given tacrine in first period (days 1-28) and placebo in second (days 29-56); group 2 given placebo in first period and tacrine in second.

† Hepatitis noted during placebo period, after finishing with tacrine.

TABLE V—Results of main cognitive and behavioural evaluations during follow up study of 49 patients with Alzheimer's disease (22 given placebo, 27 given tacrine). Values are means (SD)

	Baseline*	Crossover*	Month 3	Month 4	Month 5	Month 6
<i>Mini mental state score</i>						
Placebo	13.7 (5.8)	14.9 (6.4)	16.3 (6.4)	15.2 (7.0)	14.9 (6.6)	14.9 (6.6)
Tacrine	15.0 (6.2)	17.2 (6.9)	17.2 (6.2)	16.7 (6.6)	17.4 (7.3)	17.1 (7.1)
<i>Stockton geriatric score</i>						
Placebo	33.9 (19.8)	30.2 (15.7)	32.4 (18.8)	33.0 (18.0)	31.8 (18.2)	34.2 (17.8)
Tacrine	23.4 (13.6)	21.7 (13.8)	19.7 (13.0)	19.0 (12.7)	20.5 (13.8)	22.3 (13.3)

\* Means of values obtained at baseline and at end of period of treatment (28 or 56 days) chosen by patients (tacrine or placebo).

interval -5.43 to 5.46), and the mean rise in the Stockton geriatric score was 0.44 (95% confidence interval -11.81 to 12.69).

The visual analogue scales measuring subjective impressions of overall efficacy and tolerance of tacrine or placebo were scored higher by the patient's relative than by the physician. As scored by the physician, efficacy was greater with tacrine than with placebo (mean score 11.6 (17.9) with tacrine *v* 6.3 (10.2) with placebo; mean difference 5.2 (15.2), *t*=2.66, *p*=0.01). No significant improvement was detected by any relative (18.8 (20.5) with tacrine *v* 15.4 (18.2) with placebo; mean difference 3.4 (21.3), *t*=1.22, *p*=0.22). Comparison of the scores for side effects (that is, tolerance) by the physicians and relatives showed in both cases significantly lower levels of tolerance of tacrine than placebo (mean score by physicians 13.7 (21.7) during the tacrine period *v* 3.9 (12.7) with placebo (mean difference 9.8 (24.1), *t*=3.13, *p*=0.003); mean score by relatives (18.3 (25.0) during the tacrine period *v* 4.9 (12.5) with placebo (mean difference 13.4 (24.5), *t*=4.23, *p*<0.001)).

As the severity of Alzheimer's disease might have influenced the results, we compared the changes in mini mental state scores in the three grades of severity defined by the DSM-III-R. The mean changes in mini mental state scores were -0.37 (2.9), 0.40 (2.9), and -0.13 (2.4) in mild, moderate, and severe dementia respectively (*F*=0.44; *p*=0.66). Plasma tacrine concentrations in the 22 patients in whom they were assayed ranged from 49 to 1140 mmol/l (mean 379 (311) mmol/l). The mean initial mini mental state score in these patients was slightly higher than that in the other 38 (15.9 (5.7) *v* 12.5 (6.3); *t*=2.06, *p*=0.044). No correlation was found between the scores on the mini mental state scale, Stockton scale, or visual analogue scale scored by the physician and the plasma tacrine concentrations.

**Tolerance**—Of the seven patients who dropped out of the trial, one withdrew for personal reasons not related to the treatment and six were excluded because of high liver enzyme activities. Two other patients had raised liver enzyme activities at the end of the eight week crossover study, but as they completed all evaluations they were included in the statistical analysis. Table IV gives the main findings in these eight patients. The patient with the highest liver enzyme activities (a 76 year old woman) was admitted to an intensive care unit. Liver biopsy showed extensive centralobular necrosis without steatosis consistent

with acute cytolytic hepatitis. In all the patients with hepatitis liver enzyme values returned to normal three to four weeks after withdrawal of tacrine and remained in the normal range six to 12 months later. Moderate gastrointestinal side effects (nausea or vomiting, or both) were experienced by 24 of the 60 patients. In 20 they occurred during the tacrine treatment period and in four during the placebo period. During the tacrine treatment period one patient complained of headache and two complained of fatigue in addition to gastrointestinal side effects. No changes in blood pressure or heart rate were noted.

**Follow up study**—At the end of the crossover study the patients were free to continue the treatment for four more months. Three patients were withdrawn at the end of the crossover study (two because of hepatitis, one because of confusion). Only five patients decided not to participate in the follow up study. They had a lower mini mental state score (9.8 (7.4) *v* 14.5 (6.0); *t*=1.62, *p*=0.10) and a higher Stockton geriatric score (40.8 (19.7) *v* 27.9 (17.2); *t*=1.58, *p*=0.11) than the 52 patients who agreed to take part. At this stage the physician in charge asked the relative or patient, or both, to guess which period of treatment (tacrine or placebo) had produced the greater improvement. Both the patient and the physician remained unaware of the identity of the actual drug concerned until the end of follow up. Thirty of the 52 patients chose tacrine, a proportion which did not differ from what might have occurred by chance alone. During the four months three patients were withdrawn from the tacrine treatment group (one with hepatitis (table IV), one with confusion, one with bradycardia), leaving 49 patients for the final analysis. Clinical evaluations were performed every month and biological tests every two weeks. The 27 patients assigned to receive tacrine had slightly higher initial mini mental state scores than the 22 assigned to receive placebo (15.0 (6.2) *v* 13.7 (5.8); *t*=0.79, *p*=0.43) and slightly lower Stockton geriatric scores (23.4 (13.6) *v* 33.9 (19.8); *t*=2.24, *p*=0.03). We did not find that time had any effect on these two scores (table V). Overall evaluations showed the same difference between the tacrine and placebo treatment groups as regards efficacy and the same pattern of change during the study.

## Discussion

We failed to find the strikingly beneficial effect of tacrine and lecithin reported by Summers *et al* in patients with Alzheimer's disease,<sup>1</sup> though we used a comparable methodology. A possible explanation for the discrepancy may have been the difference between the patients in the two series. All our patients met the criteria for Alzheimer's disease whereas six of the 23 patients initially studied by Summers *et al* were subsequently found not to have Alzheimer's disease. Another difference between the two series concerns the severity of dementia. All the patients studied by Summers *et al* were in institutions whereas all our patients were at home. Our patients were also younger

(mean age 66.0 years compared with 70.7). A further difference was in the dosages of tacrine used. Summers *et al* gave their patients up to 200 mg daily whereas we used a maximum of 125 mg. In our pilot study of six patients, three of whom were given 125 mg and three 200 mg, we found a small improvement only in the cognitive mini mental state score.<sup>4</sup> Using a different study design Kaye *et al*<sup>16</sup> and Gauthier *et al*<sup>17</sup> also found a small improvement only for this score. When small changes in cognitive scores are detected in series of fewer than 20 patients their relevance is questionable both clinically and statistically. Summers *et al* suggested that the patients who did not respond to tacrine in their series had insufficient concentrations of the drug in their serum.<sup>1</sup> We were able to monitor plasma tacrine concentrations in only 22 of our patients, but even in those with the highest concentrations no improvement could be detected.

Throughout the trial our patients, like those of Summers *et al*, were also given lecithin. Some workers had suggested that this compound could slightly improve the symptoms of Alzheimer's disease.<sup>18</sup> From our results we conclude that combined oral treatment with tacrine and lecithin is no more effective than treatment with lecithin alone.

There are many possible reasons for negative results in a clinical trial. The clinical severity of the disease might affect the patient's response to cholinomimetic agents, Perry *et al* having shown that the Blessed dementia score correlates with the extent of cholinergic abnormalities.<sup>19</sup> Analysis of our results, however, did not show any differential effects of tacrine on the three grades of severity of the disease as classified by the DSM-III-R. Inappropriate selection of patients and tools for evaluation may also influence the results of a trial. For instance, the study by Summers *et al* was mainly criticised for the type of patients recruited and for selecting inappropriate outcome variables.<sup>2</sup> In our study all patients met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association diagnostic criteria for possible or probable Alzheimer's disease. We used only validated cognitive and behavioural evaluation scales and defined only two primary end points to avoid the risk of a false positive result due to multiple testing.<sup>20</sup>

It is difficult to choose a measure of efficacy, whether cognitive or behavioural. Thus Penn *et al* showed that moderate doses of intraventricular bethanechol had a palliative effect on mood and behaviour but not on cognitive function.<sup>21</sup> We used both cognitive and behavioural tests but did not find any improvement. Using an analogue scale to assess the subjective overall efficacy of treatment with either tacrine or placebo we found that the patient's relative was more optimistic than the physician. The physician scored tacrine significantly higher than placebo as regards efficacy whereas the patient's relative did not. Nevertheless, as one third of the patients experienced gastrointestinal side effects with tacrine evaluation might not have been properly blinded. Finally, when we asked the patient or his or her relative, or both, to guess which period of treatment (tacrine or placebo) had induced the maximum improvement the proportions who chose tacrine and placebo were comparable.

A washout period between the two treatment periods of the trial would have been appropriate to minimise carryover effects. No such effects were detected neurologically, but two patients developed hepatitis during the placebo period, after finishing with tacrine. Most trials have been criticised because the period of treatment was too short. In our series 49 of the 60 patients who completed the crossover study were given the treatment that they preferred for a further four months. Tacrine evidently did not have more effect

than placebo, though we assume that the patients who chose tacrine were the more responsive to the drug. At the level of the whole series of patients the most likely explanation for our negative results is the absence of efficacy of tacrine with lecithin.

We found an increase in liver enzyme activities in nine of 67 patients, and this was also found in 17 of the 50 patients studied by Gauthier *et al*.<sup>17</sup> This side effect led to the discontinuation of the large American trial, which was subsequently resumed with smaller dosages of tacrine.<sup>13</sup> In our patients hepatic side effects were mainly seen early in the trial. Liver toxicity was not dependent on variables such as age, dosage, or renal function. Ames *et al* performed a liver biopsy in a 61 year old woman with a mild increase in liver enzyme values and found a pattern consistent with drug induced granulomatous hepatitis.<sup>22</sup> We performed a liver biopsy in a patient with a much larger rise in hepatic enzyme values than in their patient and found hepatocellular necrosis. All our patients with hepatitis had normal liver function values six months after stopping tacrine or placebo.

Gastrointestinal side effects were common, roughly one third of our patients experiencing nausea or vomiting, or both. In the study by Gauthier *et al* 80% of patients suffered autonomic side effects, whose frequency was not reduced by a peripheral muscarinic blocker.<sup>17</sup> One of our patients presented with bradycardia, which has been reported before with tacrine.<sup>23</sup>

We conclude that combined oral treatment with tacrine and lecithin does not improve the cognitive or behavioural symptoms of patients with Alzheimer's disease. As tacrine also carries a high risk of potentially lethal hepatitis, its use cannot be recommended.

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## Risk of malaria in British residents returning from malarious areas

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### Abstract

**Objectives**—To identify which British residents travelling abroad are at greatest risk of malaria infection, and to determine the efficacy of malaria chemoprophylaxis for preventing *P falciparum* infections in tropical Africa.

**Design**—Prospective cohort study (case-base linkage) with routine national surveillance systems. Denominators (base population) were obtained from monitoring a random sample of returning British travellers with the international passenger survey. Numerators (cases) were obtained from reports of malaria infections in British residents, through the Malaria Reference Laboratory network.

**Setting**—International passenger survey conducted at passport control of international airports in Britain. Malaria reports received nationally were collated centrally in London.

**Subjects**—2948 British residents (0.2%) returning to Britain in 1987 randomly selected and questioned and 1052 British residents with microscopically confirmed malaria infections in 1987, whose case reports were reviewed and on whom additional data were collected by postal survey.

**Main outcome measures**—Annual incidence subdivided by categories of risk. Chemoprophylactic efficacy for east and west Africa by principal regimens and compliance.

**Results**—Annual rates of reported infection per 100 000 travellers to Oceania were 4100; to west and east Africa were 375 and 172 respectively; to Latin America, the Far East, and the Middle East were 12, 2, and 1 respectively. Immigrants visiting friends and relatives in Ghana and Nigeria were at greatest risk (1303 and 952 per 100 000 respectively) in west Africa. Business travellers to Kenya experienced the highest attack rates in east Africa (465 per 100 000). Age-sex specific attack rates varied by region. No prophylaxis was reported to have been used by 23% of British visitors to west Africa, 17% to east Africa, 46% to central or southern Africa, and 58% visiting south Asia. The efficacy of chloroquine plus proguanil against *P falciparum* infection was 73% and 54% in west and east Africa respectively. Lower values were obtained for chloroquine alone and proguanil alone. The efficacy of Maloprim (pyrimethamine-dapsone) was 61% in west Africa, but only 9% in east Africa. Visitors to west Africa who did not comply with their chemoprophylactic regimen were at a 2.5-fold higher risk of infection than fully compliant users. Non-compliant visitors to east Africa had similar rates of infection as non-drug users.

**Conclusions**—In 1987 chloroquine plus proguanil was the preferred chemoprophylactic regimen for *P falciparum* infection in Africa; antimalarial drugs must be taken regularly to be effective.

### Introduction

The control of malaria in semi-immune indigenous communities has become increasingly difficult with the spread of chloroquine resistant strains of *Plasmodium falciparum*.<sup>1</sup> There are also serious public health implications for international travellers, most of whom have no protective immunity against malaria. The reported incidence of *P falciparum* infections in Britain has risen sharply in recent years with over 1000 cases recorded by the Malaria Reference Laboratory in 1988.<sup>2</sup> The trend can be expected to continue as more travellers visit areas where the degree and intensity of transmission of resistant strains of *P falciparum* will also increase. Protection against infection in areas with a high transmission of *P falciparum* parasites has become a particular problem. Though some drugs—namely, pyrimethamine-dapsone (Maloprim), pyrimethamine-sulphadoxine (Fansidar), and amodiaquine—have offered greater protection against infection than chloroquine or proguanil, the risk of serious adverse reactions associated with their use has been considered to be unacceptable in otherwise healthy subjects, unless the risk of a potentially fatal infection is high.<sup>3,4</sup> Chloroquine plus proguanil has thus been the principal regimen advised for British travellers visiting areas of sub-Saharan Africa, the origin of over 80% of *P falciparum* infections imported into Britain.<sup>5</sup> It is not known, however, how much protection this regimen now offers non-immune visitors exposed to *P falciparum* infections. Early formulation of this regimen originated from one retrospective cohort study conducted between 1978 and 1983, which illustrated empirically that 200 mg of proguanil daily, alone and combined with chloroquine, was a highly effective regimen in east Africa.<sup>6</sup> Although more recent prospective cohort studies have been performed, efficacy data generated from these studies have not been adequate to guide current recommendations.<sup>7-9</sup> The limitations of such cohort studies are now well recognised; they can be expected to provide data on efficacy only for select populations at very high risk of malaria (above 1%), if drug prophylaxis is controlled, and when the diagnoses are verified microscopically.<sup>10</sup> Data on the risk of infection with malaria in different subgroups and the relative efficacy of chemoprophylactic regimens under varying epidemiological conditions are, however, required to ensure that recommendations for chemo-

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